

surgical and medical treatments directed at removal or dissolution of clots are also likely to be of great benefit in the treatment of this common and devastating disease.

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Chasing Mutations in the Epidermal Growth Factor in Lung Cancer

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Non-small-cell lung cancer is the leading cause of death from cancer in men and women in the United States, and worldwide it kills more than 1 million people annually. Approximately two thirds of patients with non-small-cell lung cancer present with locally advanced or metastatic disease that requires systemic therapy in addition to surgery or radiation therapy. The good news is that the results of systemic therapy are improving: chemotherapy prolongs survival and improves the quality of life for patients with non-small-cell lung cancer. The bad news is that systemic therapy is still woefully inadequate: only 30 to 40 percent of patients with metastatic non-small-cell lung cancer survive for even one year.

For this reason, the finding that therapy targeted against the epidermal growth factor receptor (EGFR) had substantial clinical benefits in 10 to 20 percent of patients with non-small-cell lung cancer was of great interest. An important example of targeted therapy that is revolutionizing cancer treat-

ment is imatinib, which inhibits the ABL tyrosine kinase that is activated by the *BCR-ABL* translocation in chronic myeloid leukemia, and *c-kit*, which is activated by a somatic mutation in gastrointestinal stromal tumors.

EGFR, a receptor tyrosine kinase, is frequently overexpressed and activated to a phosphorylated state in non-small-cell lung cancer. The tyrosine kinase activity of phosphorylated EGFR in cancer cells results in the phosphorylation of downstream proteins that incite cell proliferation, invasion, metastasis, and inhibition of apoptosis. Because several cancers overexpress EGFR, this tyrosine kinase has been a favorite target for treatment. Two oral anilinoquinazoline EGFR tyrosine kinase inhibitors, gefitinib (Iressa) and erlotinib (Tarceva), have been approved in the United States for use as second-line or third-line therapy in advanced non-small-cell lung cancer. In comparison with placebo, treatment with erlotinib improved one-year survival rates, from 22 to 31 percent, in patients with non-

small-cell lung cancer who had progressive metastatic disease after receiving other chemotherapy. Particularly tantalizing were the occasionally dramatic clinical responses that were durable (i.e., lasted several years). This past year, two groups of investigators simultaneously reported the important discovery that most patients who had a response to gefitinib had tumors with somatic mutations of *EGFR* — small deletions, insertions, or point missense mutations — that affect critical amino acids in the ATP-binding cleft of the tyrosine kinase domain of the receptor.^{1,2} This very cleft is the binding site for the inhibitor drugs. These *EGFR* mutants have increased and prolonged tyrosine kinase activity in response to the ligand (epidermal growth factor) and are exquisitely sensitive to anilinoquinazoline *EGFR* inhibitors. This phenomenon is an example of what Bernard Weinstein called “oncogene addiction.”³ The abnormality of the oncogene drives the cell toward malignancy and, in so doing, alters cell-signaling pathways in a way that makes the cell absolutely dependent on the oncogene for its survival. Weinstein playfully pointed out that this dependence was the cancer’s Achilles’ “heal,” and thus the general strategy is to discover mutated oncogenes and develop drugs targeted to their protein products. This concept underlies the present thinking about *BCR-ABL*, mutated *c-kit*, *phosphatidylinositol-3 kinase* mutations in colon cancer, occasional *HER2/neu* (also called *ERBB2*) mutations in lung cancer, and genome-wide searches for mutations through the sequencing of all tyrosine kinases or all kinases in various cancers. Any of these kinases that in the mutated form have oncogenic effects become important new “druggable” targets.

Despite the successes of targeted therapy, clinicians know that the tumors eventually became resistant to the treatment. Detailed molecular studies in chronic myeloid leukemia showed that resistance to imatinib was often associated with a mutation in the *BCR-ABL* fusion gene, and saturation analysis allowed the identification of all such mutants.⁴ However, the real importance of the discovery of these new mutations was that new drugs could be designed and identified to inhibit the resistant receptor, thereby allowing effective second-line therapy to be directed at the same target.

In this issue of the *Journal*, Kobayashi et al.⁵ show that the same principle holds for non-small-cell lung cancer that has become resistant to therapy targeted to a mutated *EGFR*. The investigators

performed a second biopsy in a patient with non-small-cell lung cancer whose tumor had one of the mutations that increase the susceptibility to gefitinib. This tumor had progressed after a two-year response to gefitinib, and the biopsy specimen contained a second mutation in the tyrosine kinase domain of *EGFR*. Elegant molecular, biologic, and computer-modeling studies showed that this second mutation replaced threonine with methionine at position 790 (T790M) in the catalytic cleft of the *EGFR* tyrosine kinase domain, thereby preventing the access of gefitinib to the gefitinib-binding site while preserving the kinase activity of the ligand after ligand stimulation. Thus, the oncogenic function of the mutated *EGFR* was retained, but the ability of gefitinib or erlotinib to bind to the receptor by a second mutation was lost. The investigators screened other *EGFR* inhibitors with different molecular structures and found at least one that inhibited the newly mutated receptor. Their modeling studies provide a molecular rationale for the selection of such a new drug.

The story is even more interesting, because the T790M *EGFR* mutation corresponds structurally to the threonine-to-isoleucine mutation at position 315 of *BCR-ABL*, which commonly confers resistance to imatinib in chronic myeloid leukemia. This type of change had already been introduced into *EGFR* two years previously by other investigators, who found that it caused resistance to anilinoquinazolines.⁶ This finding suggests that there are mechanisms of drug resistance common to tyrosine kinase inhibitors that could be predicted from the start. We should also recognize that the drug-resistance mutation can occur in either the originally mutated *EGFR* or the wild-type allele in the tumor. *EGFR* receptors form homodimers and heterodimers; dimerization of an *EGFR* carrying a drug-resistance mutation in a wild-type allele with the oncogenic *EGFR* could affect the function of the oncogenic receptor.

It will be important to discover at what stage, in the pathogenesis of lung cancer, *EGFR* mutations occur. If they are found in preneoplastic lesions, it may be possible to screen for them and, if they are present, to use relatively nontoxic tyrosine kinase inhibitors as chemopreventive agents. Most non-small-cell lung cancers do not have these mutations but, rather, overexpressed and activated phosphorylated *EGFR*. Clinical trials suggest that some of these tumors are also responsive to tyrosine kinase

inhibitors. More intriguing is the possibility that a “synthetic lethal” approach can be developed as a variation on the theme of oncogene addiction. In this scheme, the cancer cell requires not only activated wild-type phosphorylated EGFR-mediated signaling (which can be treated with tyrosine kinase inhibitors) but also a minimum of one other pathway. If these second pathways could be identified and proteins within them “drugged,” perhaps non-small-cell lung cancers could have molecularly targeted therapy.

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